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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.	OCR-729/756
First Inventor or Application Identifier	John Wood
Title	Glycosylated Indolocarbazole Synthesis
Express Mail Label No.	EL308939123US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. * Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original and a duplicate for fee processing)
2. Specification [Total Pages 31]
 - Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R & D
 - Reference to Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. Drawing(s) (35 U.S.C. 113) [Total Sheets]
4. Oath or Declaration [Total Pages]
 - a. Newly executed (original or copy)
 - b. Copy from a prior application (37 C.F.R. § 1.63(d))
(for continuation/divisional with Box 16 completed)
 - i. DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).

* NOTE FOR ITEMS 1 & 13: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

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Washington, DC 20231

5. Microfiche Computer Program (Appendix)
6. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
 - a. Computer Readable Copy
 - b. Paper Copy (identical to computer copy)
 - c. Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

7. Assignment Papers (cover sheet & document(s))
8. 37 C.F.R. § 3.73(b) Statement Power of
(when there is an assignee) Attorney
9. English Translation Document (if applicable)
10. Information Disclosure Statement (IDS)/PTO-1449 Copies of IDS
Citations
11. Preliminary Amendment
12. Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
13. * Small Entity Statement(s) Statement filed in prior application,
(PTO/SB/09-12) Status still proper and desired
14. Certified Copy of Priority Document(s)
(if foreign priority is claimed)
15. Other:

16. If a CONTINUATING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:

Continuation Divisional Continuation-in-part (CIP) of prior application No. 09 / 206,082

Prior application information: Examiner L. Stockton Group / Art Unit: 1613

For CONTINUATION or DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 4b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

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Separator Sheet



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Application Text

Place Papers behind this sheet in the following order:

1. Preliminary Amendment
2. Specification (English Language Only)
3. Claims
4. Abstract

GLYCOSYLATED INDOLOCARBAZOLE SYNTHESIS

Related Application Data

This is a continuation-in-part of co-pending U.S. application serial number 08/817,230, filed June 4, 1997 as the U.S. national phase entry under 35 U.S.C. 371 of PCT/IB96/00987, which had an international filing date of August 9, 1996, claiming benefit of U.S. application serial number 60/002,164 filed August 11, 1995, all of which are incorporated herein in their entireties by reference.

Technical Field of the Invention

This invention relates to the synthesis of tertiary alcohols by coupling of diazo carbonyl compounds with allylic alcohols under conditions that produce carbene or carbenoid intermediates. Both furanosylated and pyranosylated indolocarbazoles are prepared, including naturally occurring compounds as well as a range of structurally diverse analogues.

Background of the Invention

Originally discovered in the course of screening for microbial alkaloids, staurosporine and structurally related compounds have been the object of considerable investigation for various biomedical purposes for the past twenty years (for a review, see Omura, *et al.*). It has been recently reported that staurosporine and its derivatives, for example, inhibit smooth muscle contraction, platelet aggregation, neurotrophic activity, and, most importantly, protein kinases *in vitro* and *in vivo* (*ibid.*).

Disruption of cellular signal transduction via kinase malfunction has been related to the onset of several disease states, including rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus and Alzheimer's disease. For example, the clinical severity of Alzheimer's disease correlates well with the formation of amyloid plaques and neurofibrillary tangles; both manifest paired helical filaments (PHF) that

possess an overphosphorylated microtubule associated protein (M.A.P., also known as τ -protein). It has been suggested that overphosphorylation may lead to conformational changes that inhibit τ binding to microtubules. Recently, a bovine τ -kinase denominated PK40 (molecular weight 40,000) has been isolated and shown to induce a gel mobility shift of PHF- τ . PK40 is not closely associated with the cytoskeleton and appears to be a member of the extracellular regulated kinases. Specific inhibition of enzymes like PK40 by small, orally bioavailable compounds, promise to be a highly successful means of treating Alzheimer's disease.

Unfortunately, the structural homology shared by the many kinase isozymes has impeded the development of selective and therapeutically useful inhibitors. It would be desirable to have others.

Summary of the Invention

It is a specific objective of the invention to provide a synthesis for (+)- and (-)-K252a, analogues of K252a, staurosporine and its congeners, (+)-RK286c and (-)-RK286c, (+)-MLR52 and (-)-MLR52, (+)-TAN 1030a and (-)-TAN 1030a, (+)-UNC-01 and (-)-UNC-01, (+)-RK1409 and (-)-RK1409, and the like.

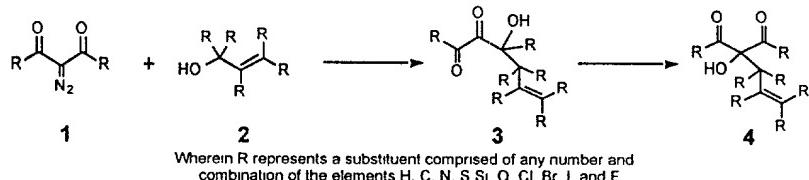
It is another and more general object of the invention to provide for the synthesis of furanosylated and pyranosylated indolocarbazoles, particularly the interconversion of furanosylated indolocarbazoles to the corresponding pyranosylated derivatives.

It is a further objective of the invention to provide an efficient approach to the synthesis of enantioenriched tertiary alcohols.

These and other objectives are accomplished by the present invention, which provides a process for the preparation of tertiary alcohols containing the structural features illustrated in **3** or **4** below (Scheme I). The process utilizes at least one carbonyl compound, e.g., **1** in Scheme I) and at least one allylic alcohol (e.g., **2** in Scheme I) in a coupling reaction that is run under conditions that produce carbene or carbenoid intermediates from the diazo-containing substrate. These conditions include transition metal catalysis or either thermal or photochemical decomposition.

In some preferred embodiments illustrated hereafter, Rh₂(OAc)₄ is employed to catalyze the coupling reaction.

Scheme I



Wherein R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, and F

As used herein, terminology referring to R as representing a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I and F refers, as is known to those skilled in the art, to alkyl, alkenyl, alkynyl, aryl, cyclic or heterocyclic substituents comprised of these elements that may be alkaloid substituents. The definition encompasses the following R groups:

- a) a C₃₋₁₀ branched or unbranched alkyl, alkenyl, or alkynyl, which may be partially or fully silylated or halogenated, or combinations thereof, and optionally substituted by one to three substituents consisting of aryl or heteroaryl, wherein the aryl or heteroaryl rings may be optionally substituted with one to five groups consisting of either C₁₋₆ branched or unbranched alkyl, which may be partially or fully halogenated, C₃₋₈ cycloalkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy, which may be partially or fully halogenated, nitro, amino, alkylamino, dialkylamino, carbonylamine, carbonyldialkylamine, carboxy, carbonyloxy C₁₋₄ branched or unbranched alkyl;
- b) a C₃₋₁₀ branched or unbranched cycloalkyl which may be partially or fully silylated or halogenated, or combinations thereof, and optionally substituted by one to three substituents consisting of aryl or heteroaryl, wherein the aryl or heteroaryl rings may be optionally substituted with one to five groups consisting of either C₁₋₆ branched or unbranched alkyl, which may be partially or fully halogenated, C₃₋₈ cycloalkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy, which may be partially or fully halogenated, nitro, amino, alkylamino, dialkylamino, carbonylamine, carbonyldialkylamine, carboxy, carbonyloxy C₁₋₄ branched or unbranched alkyl;
- c) a C₅₋₈ branched or unbranched cycloalkenyl which may be partially or fully silylated or halogenated, or combinations thereof, and optionally substituted by one to three substituents consisting of aryl or heteroaryl, wherein the aryl or heteroaryl rings

may be optionally substituted with one to five groups consisting of either C₁₋₆ branched or unbranched alkyl, which may be partially or fully halogenated, C₃₋₈ cycloalkyl, halo, hydroxy, cyano, C₁₋₃ alkyloxy, which may be partially or fully halogenated, nitro, amino, alkylamino, dialkylamino, carbonylamine, carbonyldialkylamine, carboxy, carbonyloxy C₁₋₄ branched or unbranched alkyl;

d) an aryl or heteroaryl optionally substituted with one to five groups consisting of either aryl, heteroaryl, C₁₋₆ branched or unbranched alkyl, which may be partially or fully silylated or halogenated, C₃₋₈ cycloalkyl, C₁₋₅ alkylaryl, halo, hydroxy, cyano, C₁₋₃ alkyloxy, which may be partially or fully halogenated, aryloxy, heteroaryloxy, nitro, amino, alkylamino, dialkylamino, arylamino, heteroaryl amino, carbonylamine, carbonyldialkylamine, carboxy, carbonyloxy C₁₋₄ branched or unbranched alkyl, C₁₋₅ alkylcarbonyl C₁₋₄ branched or unbranched alkyl, C₁₋₅ alkyl or alkenylcarboxy, C₁₋₅ alkylamine, C₁₋₅ alkylodialkylamine, C₁₋₅ alkylthio, C₁₋₅ alkylsulfinyl, C₁₋₅ alkylsulfonyl, sulfonylamine, sulfonyldialkylamine;

(e) carboxy, carbonyloxy C₁₋₄ branched or unbranched alkyl, C₁₋₅ alkylcarbonyl C₁₋₄ branched or unbranched alkyl, C₁₋₅ alkyl or alkenylcarboxy, aryloxy, heteroaryloxy, nitro, amino, alkylamino, dialkylamino, arylamino, heteroaryl amino, carbonylamine, carbonyldialkylamine C₁₋₅ alkylamine, C₁₋₅ alkylodialkylamine, C₁₋₅ alkylthio, C₁₋₅ alkylsulfinyl, C₁₋₅ alkylsulfonyl, sulfonylamine, sulfonyldialkylamine, and partially and fully halogenated or silylated derivatives thereof;

(f) a hydrogen;

(g) a halogen;

(h) a silyl group; and

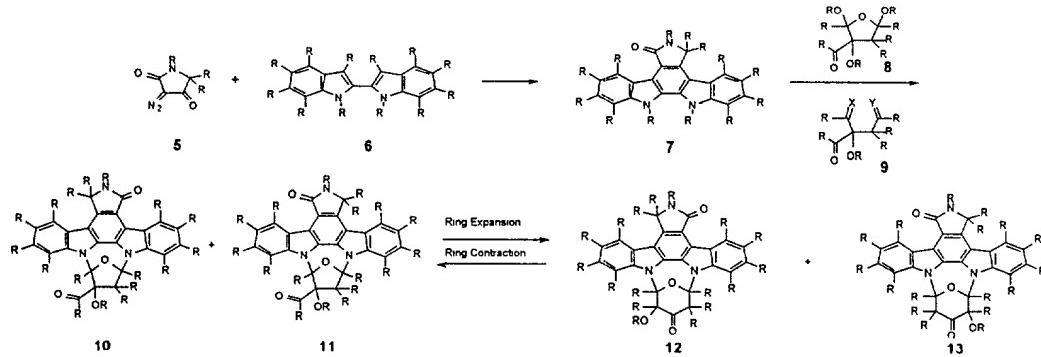
(i) mixtures of any of these.

Embodiments wherein R is H, an alkyl or an aryl are particularly preferred. In many embodiments, the R is an H or a lower unsubstituted alkyl group. As used herein, indicated above, and illustrated below, when discussing substituent R groups, the "or" indicates R groups comprising H, alkyl, or aryl groups, or mixtures of any of these. For example, the latter-mentioned subgroup encompasses alkaloids bearing

only H, only alkyl groups, and mixtures thereof. Illustrative R groups in the examples that follow are H, Me, *t*-Bu, 3,4-DMB, and PMB.

The invention more specifically provides a process for the construction of indolocarbazoles (*e.g.*, 7 below) from the coupling of diazo carbonyl compounds (*e.g.*, 5) and biindoles (*e.g.*, 6). The invention also provides a process for the stereoselective preparation of glycosylated indolocarbazoles like but not limited to 10 and 11 via furanosylation of indolocarbazoles (*e.g.*, 7) with acetals (*e.g.*, 8) or their open chain congeners (*e.g.*, 9) under conditions known to promote acetal exchange or formation, such as protic or Lewis acids.

Scheme II



As illustrated in Scheme II above, processes of the invention also provide furanosylated indolocarbazoles (*e.g.*, 10) via ring contraction of pyranosylated indolocarbazoles (*e.g.*, 12) under conditions known to effect oxidation and benzylic acid type rearrangements. The invention correspondingly provides processes for the construction of pyranosylated indolocarbazoles (*e.g.*, 12) via ring expansion of the furanosylated congeners (*e.g.*, 10).

Detailed Description of the Invention

This invention is based upon several new processes that when combined in-total or in-part can lead to the enantioselective syntheses of various indolocarbazoles.

Unless expressly noted to the contrary, the following definitions apply:

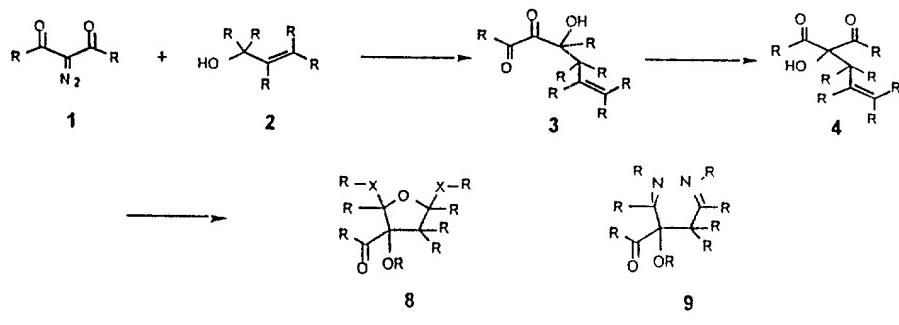
The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms. "Alkyl" refers to both branched and unbranched alkyl groups. Preferred alkyl groups are straight-chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. More preferred alkyl groups are straight chain alkyl groups containing from one to six carbon atoms and branched alkyl groups containing from three to six carbon atoms. "Alkyl", as used herein, includes unsubstituted alkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from amino, cyano, nitro, methoxy, ethoxy and hydroxy. The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Preferred cycloalkyl groups are saturated cycloalkyl groups containing from three to eight carbon atoms, and more preferably, three to six carbon atoms. "Alkyl" and "cycloalkyl", as used herein, include unsubstituted alkyl and cycloalkyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from halo, amino, cyano, nitro, methoxy, ethoxy and hydroxy. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkylthio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom.

The terms "alkenyl" and "alkynyl" refer to mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms, containing at least one double or triple bond, respectively. "Alkenyl" and "alkynyl" refer to both branched and unbranched alkenyl and alkynyl groups. Preferred alkenyl and alkynyl groups are straight chain alkenyl or alkynyl groups containing from two to eight carbon atoms and branched alkenyl or alkynyl groups containing from five to ten carbon atoms. More preferred alkenyl and alkynyl groups are straight chain alkenyl or alkynyl groups containing from two to six carbon atoms and branched alkenyl or alkynyl groups containing from five to eight carbon atoms. The term "cycloalkenyl" refers to the cyclic analog of an alkenyl group, as defined above. Preferred cycloalkenyls include cycloalkenyl rings containing from three to eight carbon atoms, and more preferably, from three to six carbon atoms. "Alkenyl", "alkynyl" and "cycloalkenyl", as used herein, include unsubstituted alkenyl or alkynyl radicals, those radicals that are partially or fully halogenated and those radicals substituted with one to four, preferably one or two, substituents selected from halo, amino, cyano, nitro, methoxy, ethoxy and hydroxy.

The term "aryl" refers to an aromatic carbocyclic radical having from 5 to 8 carbon atoms if monocyclic and from 8 to 12 carbon atoms if bicyclic. Preferred aryl radicals include phenyl and naphthyl. The term "heteroaryl" refers to any aryl radical in which one or more carbon atoms are replaced with a heteroatom. The terms "aryl" and "heteroaryl" also refer to partially or fully halogenated aryl and heteroaryl groups substituted with halo, alkyl; hydroxyl; nitro; -COOH; -CO(lower alkoxy); CO(lower alkyl); amino; alkylamino; dialkylamino; alkoxy; -NCOH; -NCO(lower alkyl); -NSO₂-Ph(halo)₀₋₃, Ph; -O-Ph; naphthyl; -O-naphthyl; pyrrolyl; pyrrolyl substituted with lower alkyl; pyridyl; pyridinyl; pyrazinyl; pyrimidinyl and pyridazinyl.

As summarized above, in a practice of the invention at least one diazo carbonyl compound and at least one allylic alcohol of structures 1 and 2, respectively (Scheme III), are combined to produce tertiary alcohols of structures 3 and/or 4 in Scheme III. A preferred embodiment employs but is not limited to the use of transition metal catalysts in the form of ligated Rh(II) complexes, for example Rh₂(OAc)₄, to produce 3 and a Lewis acid like but not limited to BF₃•Et₂O to convert 3 to 4. In alternative embodiments the decomposition of the diazo substrate to the corresponding carbene or carbenoid involves catalysis by complexes of: Cu(II), Mn(II), Fe(II), Co(II), Ni(0), Ni(II), Zn(II), Mo(II), Ru(II), Ru(III), Bronsted and Lewis acids, thermolysis, and/or photolysis. The derived tertiary alcohols of structure 4 are further manipulated by standard chemical procedures to produce acetals of structure 8 and the corresponding open chain congeners of structure 9. The later are utilized in the furanosylation process and total syntheses described below.

Scheme III

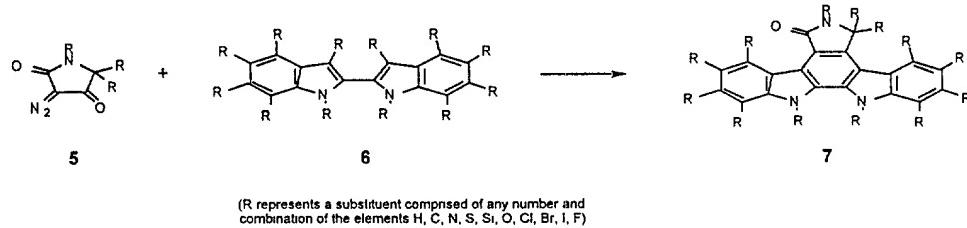


(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

(X represents S and/or O)

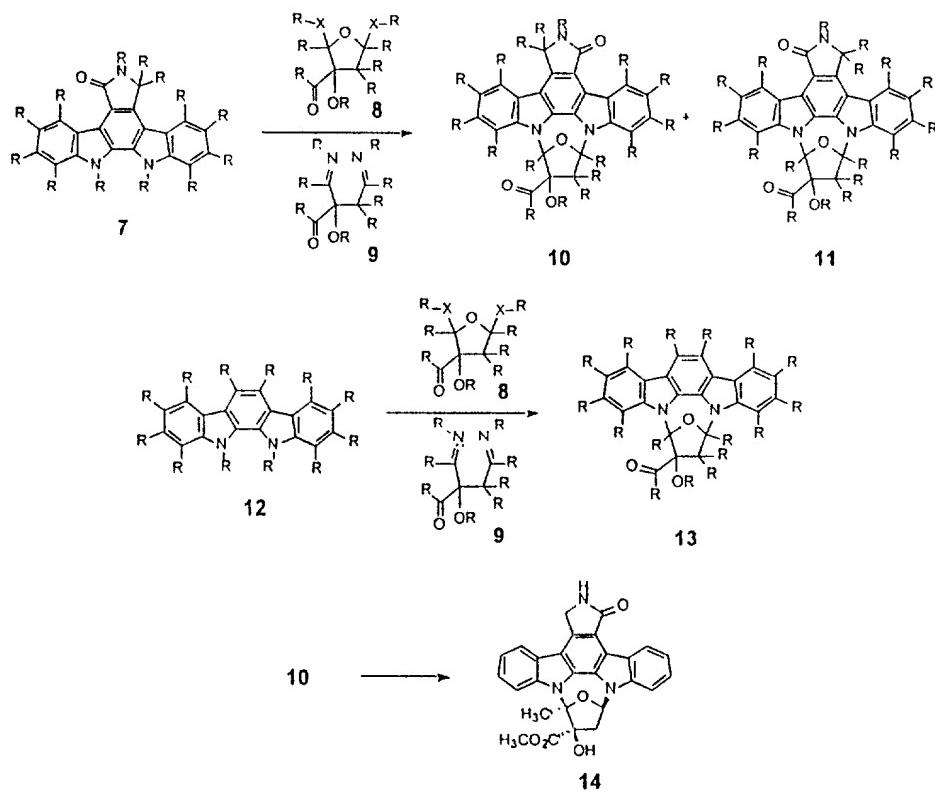
The invention also provides a process for coupling at least one diazo carbonyl compound and at least one biindole, of structures **5** and **6** respectively (Scheme IV), to produce indolocarbazoles of structure **7**. A preferred embodiment employs but is not limited to the use of transition metal catalysts in the form of ligated Rh(II) complexes, for example Rh₂(OAc)₄, in a solvent capable of solvating the substrates such as CH₂Cl₂, pinacolone, and/or CH₃CN. The reaction is carried out under conditions such that products are formed at a convenient rate such as for example about 20-30 minutes at reflux. In alternative embodiments initiating the process via decomposition of the diazo substrate to the corresponding carbene or carbenoid involves catalysis by complexes of: Cu(II), Mn(II), Fe(II), Co(II), Ni(0), Ni(II), Zn(II), Mo(II), Ru(II), Ru(III), Bronsted and Lewis acids, thermolysis, and/or photolysis.

Scheme IV



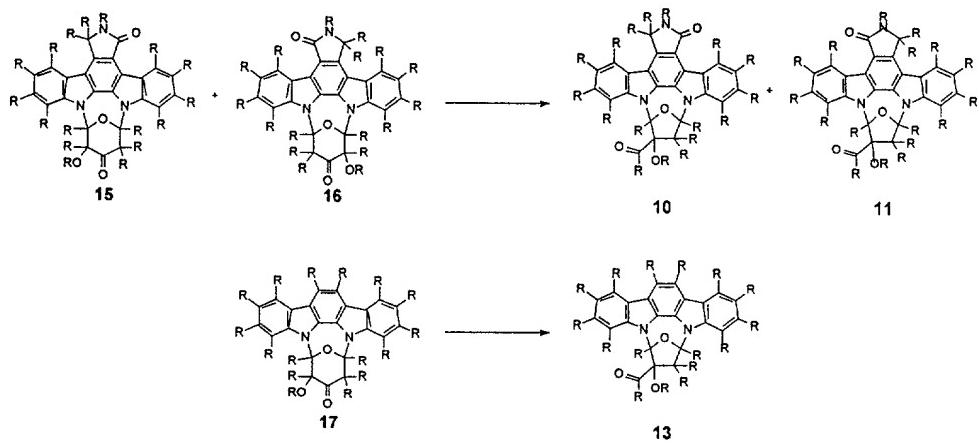
The invention also provides a process for the stereoselective furanosylation of indolocarbazoles of a structure **10** or **11** with acetals and/or their open chain congeners, of structures **8** and **9** respectively in Scheme V, under conditions that promote acetal exchange or formation, such as but not limited to Bronsted or Lewis acids such as camphor sulfonic acid (CSA), *para*-toluene sulfonic acid (PTSA), or BF₃•Et₂O (McCombie *et al.*). A preferred embodiment employs but is not limited to the use of camphor sulfonic acid (CSA) as the catalyst and the dichloroethane as the solvent in a coupling reaction that stereoselectively produces the regioisomeric furanosylated indolocarbazoles **10** and **11** in about 80% yield. The derived indolocarbazoles of structure **10** are manipulated by standard chemical procedures to produce **14** (K252a).

Scheme V



As illustrated in Scheme VI, the invention also provides a process for the ring contraction of pyranosylated indolocarbazoles of structure 15 and/or 16 to furanosylated indolocarbazoles of structure 10 and/or 11 under conditions that in single- or two-step fashion can effect oxidation and benzylic acid type rearrangement (Fredenhagen *et al.*). A preferred embodiment employs but is not limited to a single-step procedure wherein CuCl is used as both the oxidant and rearrangement promoter and methanol is used as the solvent.

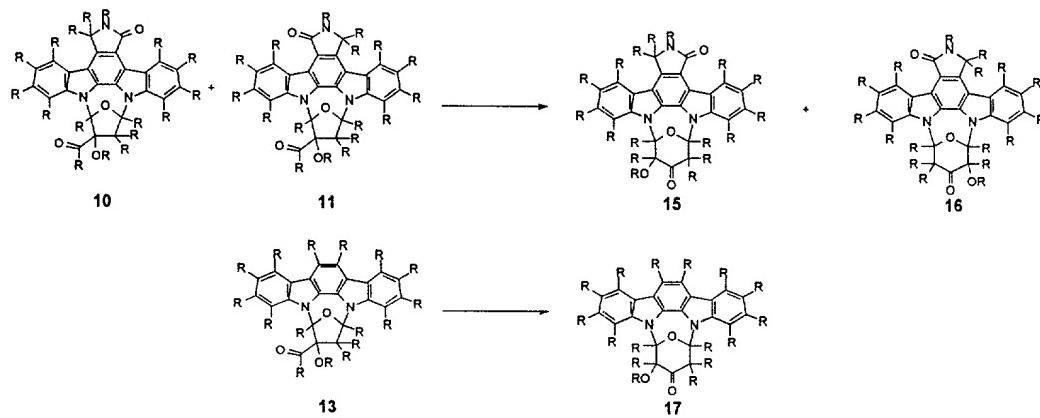
Scheme VI



(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

The invention correspondingly provides a process for the ring expansion of furanosylated indolocarbazoles of structure **10** and/or **11** to the pyranosylated congeners of structure **15** and/or **16** illustrated in Scheme VII below (Ootsuka *et al.*). A preferred embodiment employs, but is not limited to, a multistep procedure wherein **10** and/or **11** is first reduced with LiBH₄ and then the derived diol is oxidized. The resulting intermediate compound is then subjected to a Bronsted or a Lewis acid such as camphor sulfonic acid (CSA), *para*-toluene sulfonic acid (PTSA), or BF₃•Et₂O to promote ring expansion. BF₃•Et₂O is used in some preferred embodiments.

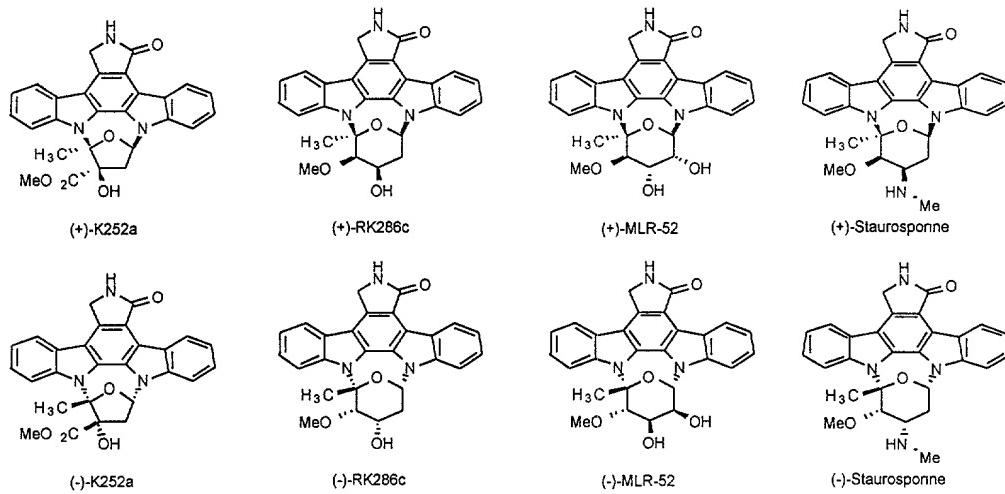
Scheme VII



(R represents a substituent comprised of any number and combination of the elements H, C, N, S, Si, O, Cl, Br, I, F)

It is an advantage of the invention that the combined processes provide efficient access to useful indolocarbazoles such as (+)- and (-)-K252a, (+)- and (-)-

RK-286c, (+)- and (-)-MLR-52, (+)- and (-)-staurosporine, and the like depicted below.



Examples

The following are presented to further illustrate and explain the present invention and should not be taken as limiting in any regard. Unless otherwise indicated, all parts and percentages are by weight and are based on the weight of the components at the indicated stage of processing. Rotations on indolocarbazole were obtained on methanol solutions. Compound structural assignments were in accord with infrared and high-field ^1H (500 MHz) and ^{13}C (125 or 62.5 MHz) NMR spectra, as well as appropriate parent identification by high-resolution mass spectrometry.

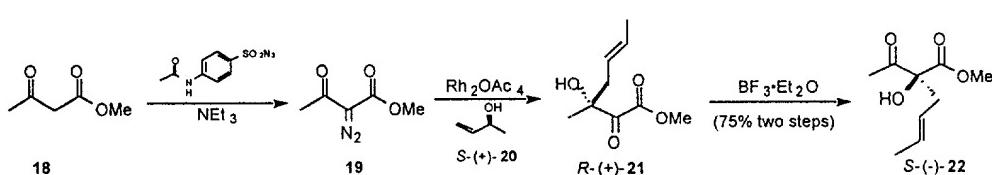
Example 1

Enantioselective Preparation of Tertiary Alcohols

This example describes a novel rhodium-catalyzed C-C bond forming reaction that allows asymmetric access to **21** (95% ee) and **22** (93% ee) in only two and three steps from methyl acetoacetate (**18**) (Scheme VIII). In this scenario α -keto ester **21** was produced from the rhodium-catalyzed decomposition of **19** in the presence of S-(+)-1-buten-3-ol (**20**) (Wood *et al.*). In the event, complete consumption of **19** was

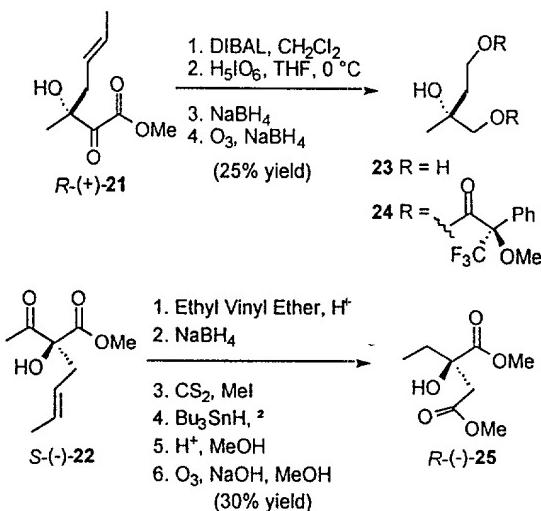
observed after only 20 minutes to reflux in benzene. Proton NMR analysis of the crude reaction indicated the clean formation of a product similar to **19**; however, the characteristic methyl ketone singlet had shifted from 2.2 to 1.5 ppm. Clearly the allyloxy or allyloxonium ylide intermediate had undergone [3,3] sigmatropic rearrangement to alcohol (+)-**21** (66% yield) (Pirrung *et al.*). Completion of the tandem rearrangement protocol was achieved by exposing (+)-**21** to $\text{BF}_3 \cdot \text{Et}_2\text{O}$ which promoted a clean [1,2]-allyl migration to furnish (-)-**22** in 74% yield. In subsequent studies, improved yields were obtained by conducting the tandem rearrangement in one pot. Thus, introducing an equivalent of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ into the cooled [3,3] reaction allows isolation of (-)-**22** in an overall yield of 75%.

Scheme VIII



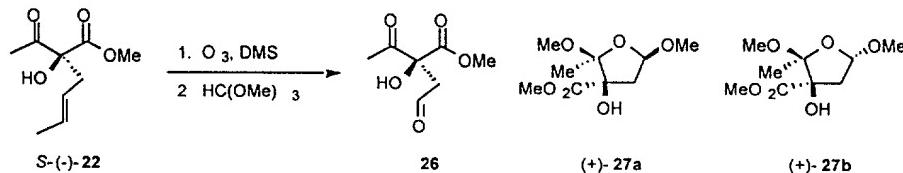
With an approach firmly established, a chemical correlation study was initiated to confirm both the sense and degree of asymmetric induction for the tandem rearrangement. Analysis of the purified products from both the [3,3] (*i.e.*, (+)-**21**) and [1,2] (*i.e.*, (-)-**22**) rearrangements via proton NMR in the presence of $\text{Eu}(\text{hfc})_4$ gave the first indication that each step was proceeding with a high degree of stereoselectivity. Conversion of (+)-**21** to **23** as outlined in Scheme IX, followed by comparison of the derived bis Mosher ester (**24**) to samples prepared from *S*-(+)- and *R*-(-)-citramalic acid, established that *S*-(+)-**20** (98% ee) had furnished *R*-(+)-**21** (95% ee). Stereoselectivity in the [1,2] shift was established by degradation of (-)-**22** to *R*-(-)**25** followed by DIBAL reduction and proton NMR analysis of the corresponding bis Mosher ester. While the Mosher ester analysis established an ee of 92%, the observation of *R*-(-)**25** in the degradation proved the absolute stereochemistry in **22** as *S*.

Scheme IX



Having established the degree and sense of asymmetric induction the asymmetric synthesis of the requisite acetals **26** and **27** was begun. Thus, reductive ozonolysis of **22** followed by acetal formation provided a ternary mixture. Spectral identification of the isolated products indicated the presence of methyl ketone **26** and furanoses **(+)-27a** and **(+)-27b** (Scheme X).

Scheme X



Example 2

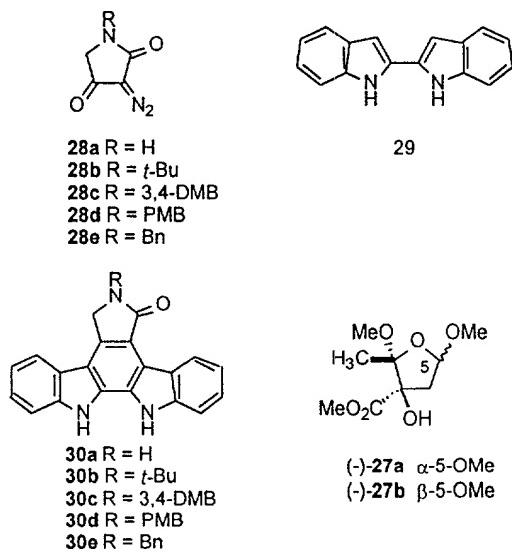
Preparation and Furanosylation of Indolocarbazoles

The Synthesis of K252a

This example describes the coupling of diazolactams **28** and 2,2'-biindole **29** to produce an intermediate that undergoes cycloaromatization to furnish the indolocarbazoles **30**. Application of this strategy allows efficient access to both the parent aglycone (**30a**) and the selectively protected derivatives (**30b-c**). Of the latter, **30c** is employed in the total synthesis of K252a. Overall, preparation of the enantioenriched furanoses **27** (described in Example 1 above) and aglycon unit **30c**

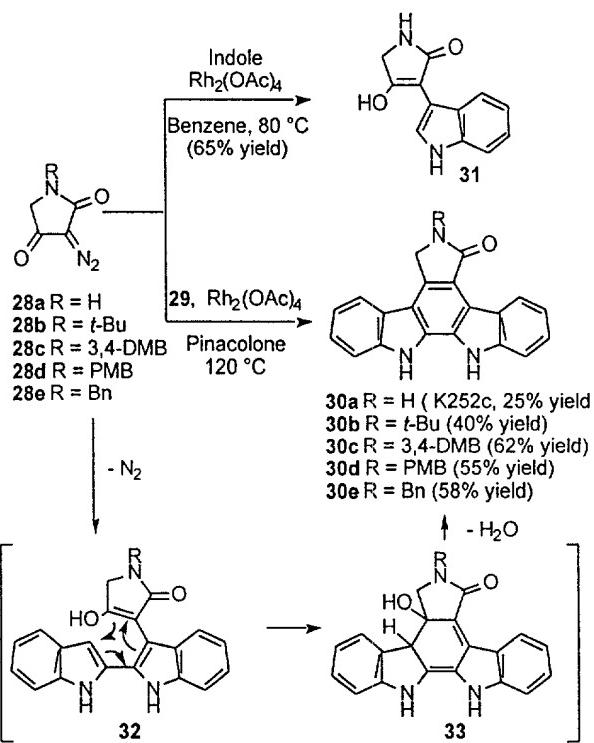
and their conversion to **14** require only eleven synthetic operations with a longest linear sequence of seven steps.

Scheme XI



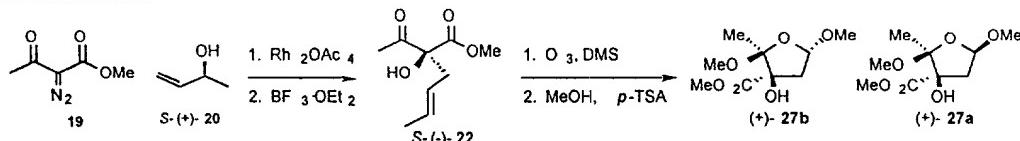
The feasibility of the carbenoid approach to **30** was initially assessed by reaction of **28a** (1.0 equiv) with indole (3.0 equiv) in the presence of catalytic Rh₂(OAc)₄ (0.01 equiv, Scheme XII). After only 12 h, TLC analysis indicated complete consumption of **28a** and standard work-up and isolation procedures furnished **31** in 65% yield. Similar conditions proved ineffective for the coupling of **28a** with **29**, and it was only after considerable experimentation that a procedure was developed which provided satisfactory yields of **30a**. The use of degassed pinacolone proved critical as this solvent was found to be both compatible with the carbenoid chemistry and capable of solvating the diindole substrate. Under these conditions the coupling of **28a** and **29** proceeded directly to **30a** (K252c) in 25% yield. Presumed intermediates **32** and **33** were not apparent by TLC or NMR analysis of the crude reaction mixture. In an attempt to complete the synthesis, the cycloglycosidation of **27** with **30a** revealed a tendency of the latter to alkylate at the amide nitrogen; thus, selectively protected aglycones **30b-e** were employed. Preparation of the corresponding diazolactams **28b-e**, followed by reaction with **29** in the presence of Rh₂(OAc)₄ (0.1 equiv) established that several protecting groups can withstand the carbenoid conditions and that the best yields (50-62%) are obtained within the benzyl class (*e.g.*, **28c,d,e** \otimes **30c,d,e** Scheme XII). To provide the most flexibility in the eventual deprotection 3,4-dimethoxybenzyl protected aglycone **28c** was employed.

Scheme XII



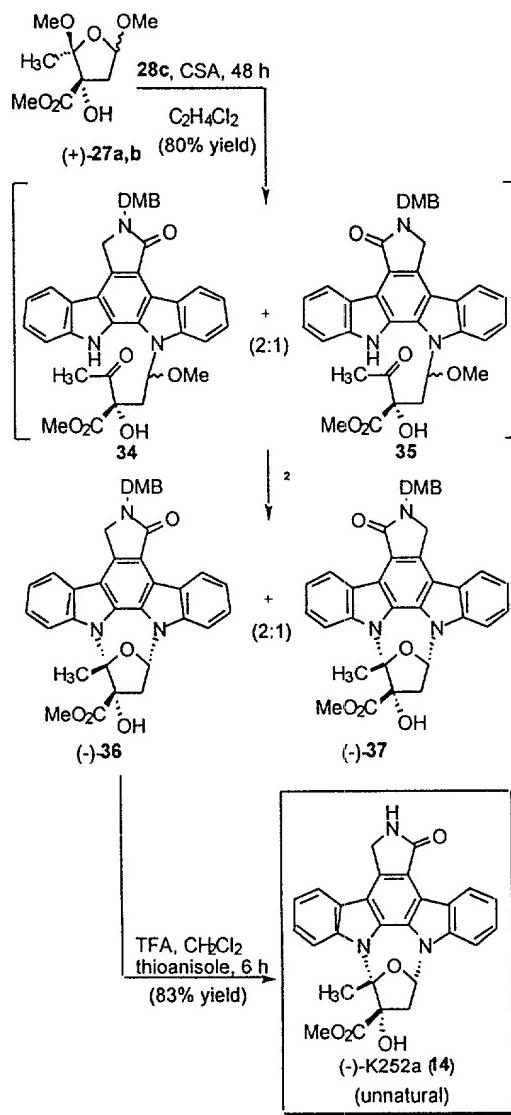
Having gained efficient access to **30c**, attention was turned to the preparation of the furanose components (**27**). To this end, a novel tandem rearrangement protocol was developed that combines methyl 2-diazo-3-oxobutyrate (**19**) and *S*-(+)-1-buten-3-ol (**20**) to furnish *(-)*-**22** in a single-pot (92% ee, 75% yield). Reductive ozonolysis of *(-)*-**22** followed by acid promoted cyclization in methanol produced *(+)*-**27a** and *(+)*-**27b** in good yield.

Scheme XIII



With both *(+)*-**27** and **30c** in hand the cycloglycosidative coupling was investigated. Of several conditions reported by McCombie, *et al.*, for related transformations, camphorsulfonic acid in 1,2-dichloroethane was found to be the catalyst and solvent of choice. In the event, **30c** and *(+)*-**27a** and **27b** combined rapidly to form two regioisomeric pairs of open chain monoamino acetal diastereomers (**34** and **35**). Prolonged heating of the quaternary mixture induced cycloglycosidation to only two of the four possible diastereomers.

Scheme XIV

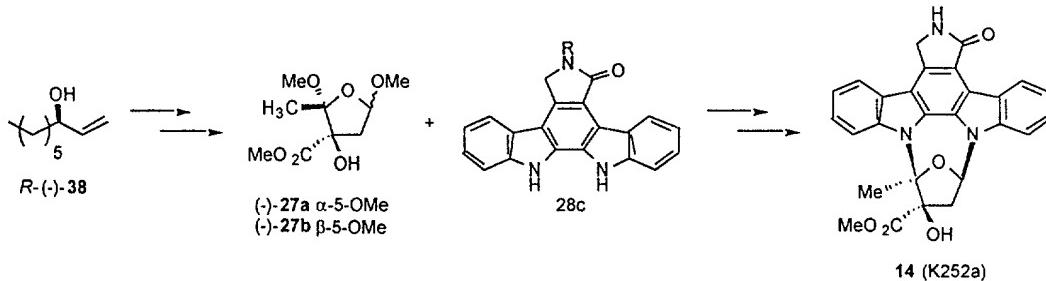


Preliminary assignment of structure was based on ^1H NMR analysis which indicated that the reaction had produced the regioisomeric products (-)-36 (55% yield) and (-)-37 (25% yield). The observed formation of (-)-14 upon deprotection of (-)-36 under standard conditions (TFA/ CH_2Cl_2 /thioanisole) established the cycloglycosidation as both regio- and stereoselective for the natural configuration. Comparison of synthetic (-)-14 to material derived from natural sources established its identity as the unnatural enantiomer of K252a.

Total synthesis of the natural enantiomer (*i.e.*, (+)-14) was effected in an analogous fashion using 28c and (-)-27a and (-)-27b as coupling partners (Scheme XV). The latter compound was prepared via the tandem [3,3]/[1,2] rearrangement

protocol (described in Example 1 above) using *R*-(*-*)-1-nonen-3-ol (**38**) as the source of asymmetry.

Scheme XV



In summary, application of a novel carbenoid mediated synthesis of K252c coupled with a highly selective tandem (3,3)/(1,2) rearrangement protocol provides efficient access to both (+)- and (−)-K252a.

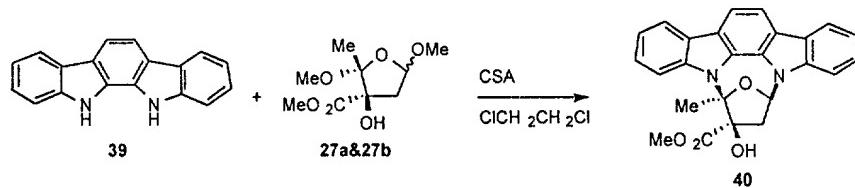
Example 3

Furanosylation of Alternative Indolocarbazoles and the Interconversion of Furanosylated and Pyranosylated Indolocarbazoles

This example reports results wherein an indolocarbazole simpler than that described Example 2 is subjected to furanosylation. The derived product **40** is further manipulated into a ring-expansion substrate **41** or **42** that undergoes conversion to the corresponding pyranosylated indolocarbazole **43** or **44**, respectively (Stoltz *et al.* 1995). It is further demonstrated in this example that the α -hydroxy ketone congener **43** undergoes facile oxidative ring contraction to the furanosylated indolocarbazole upon exposure to CuCl in methanol (Stoltz *et al.* 1996).

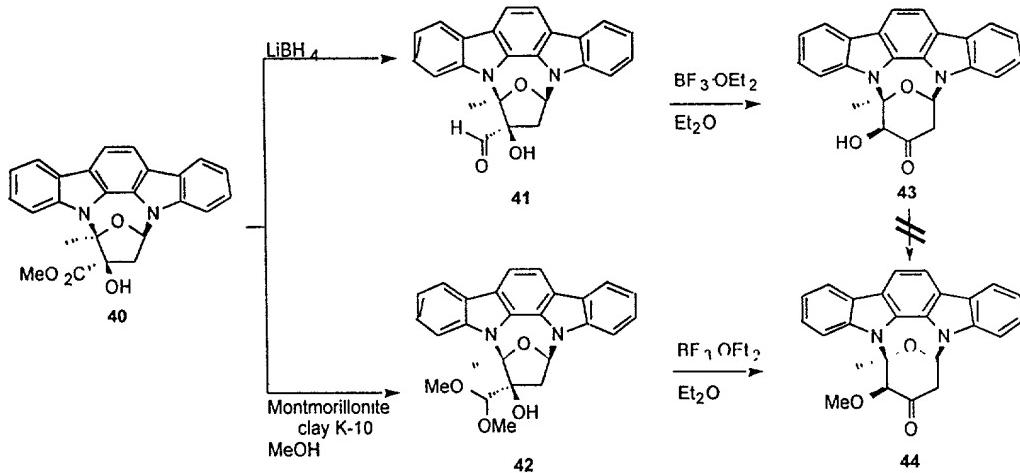
For the furanosylation, indolo [2,3-a]carbazole (**39**) was coupled with **27a** and **27b** in a manner similar to that employed in the synthesis of K252a described in Example 2. This coupling again proved highly stereoselective and produced **40** as the only isolable product in 85% yield.

Scheme XVI



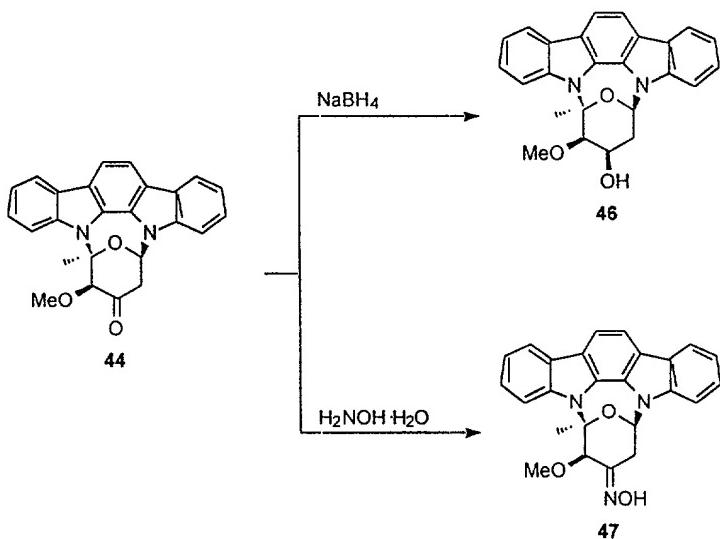
Turning to the ring expansion, it was soon discovered that transformation of **40** into aldehyde **41** followed by treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ results in a regio- and stereoselective rearrangement to the pyranosylated indolocarbazole **43**. At this stage all that remained for the preparation of **44** was what appeared to be a trivial alkylation of the C(3') hydroxyl. Ketone **43** surprisingly proved quite resistant to methylation under numerous alkylation conditions. In addition, attempts to incorporate directly the methyl substituent by promoting the rearrangement with a source of Me^+ (*e.g.*, Meerwein's reagent, TMSOTf/TMSOMe , and MeOTf) also failed. Eventually, these difficulties led to the development of an alternative strategy that targeted dimethyl acetal **42** as the substrate for a ring expansion (Scheme XVII). Although **42** was readily produced under a variety of conditions, its instability to chromatographic purification required the employment of montmorillonite clay K-10 to promote acetal formation. Removal of the clay via filtration, solvent exchange with Et_2O , and subsequent treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in the slow (72 h, 25 °C) conversion of **42** to **44** (50% yield).

Scheme XVII



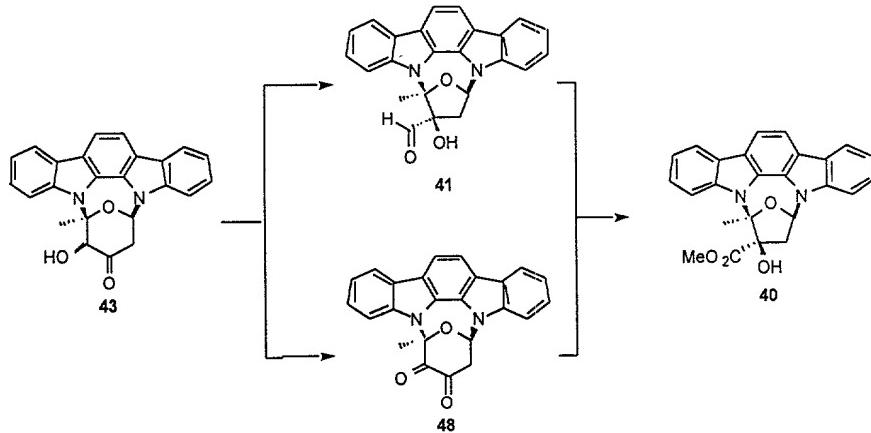
Having rapidly assembled α -methoxy ketone **44**, its conversion to the desamido pyranosylated indolocarbazoles was investigated. To this end, the analogs of RK-286c (**46**) and TAN-1030a (**47**) were readily prepared from **44** under standard conditions using NaBH₄ and H₂NOH•HCl, respectively (Scheme XVIII).

Scheme XVIII



While the above model investigations established the feasibility of a regio and stereoselective ring expansion, subsequent attempts to alkylate the derived α -hydroxy ketone **43** proved problematic. Of note is the propensity of **43** to undergo loss of the indolocarbazole nucleus as evidenced by isolation of **39** as the major product in many of the alkylation attempts. In an effort to avoid this deleterious event attention was turned to methylation procedures that appeared to proceed under essentially neutral conditions. While these efforts failed to produce any of the desired α -methoxy ketone **44**, the conditions comprising CuCl and DCC in MeOH were observed to cleanly convert **43** to **40**, the functionalized K252a sugar moiety. Apparently these conditions induced either ring contractive α -ketol rearrangement and oxidation (*i.e.*, **43**→**41**→**40**) or oxidation and ring contractive "benzilic" acid rearrangement (*i.e.*, **43**→**48**→**40**). While not wishing to be bound to any theory, since α -hydroxy aldehyde **41** failed to undergo conversion to **40** under identical conditions, the latter of these two mechanistic possibilities appears most likely. In addition, subsequent investigations have revealed CuCl in MeOH without added DCC to be the optimal conditions for converting **43** to **40** (95% yield).

Scheme XIX



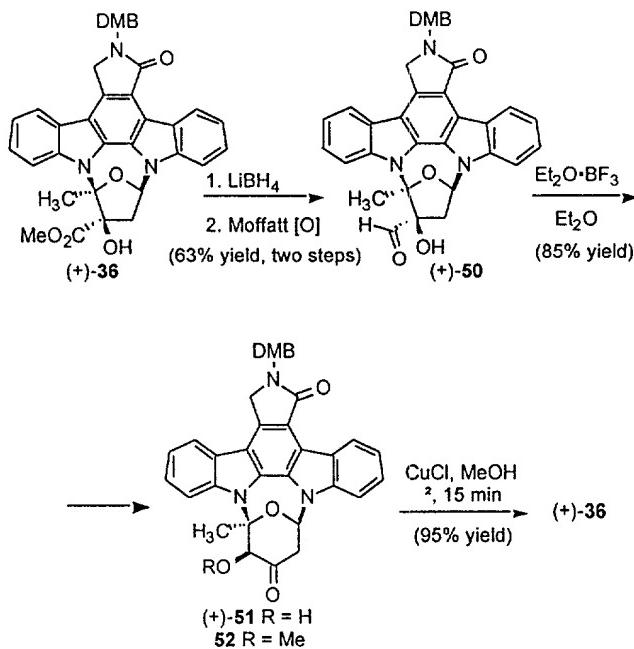
Example 4

The Synthesis of Staurosporine, RK-286c, MLR-52, and K252a

This example demonstrates that the tertiary alcohol and indolocarbazole syntheses, the indolocarbazole furansylation, and the ring-expansion protocol described in the above Examples can be used to prepare pyranosylated indolocarbazoles that are suited for conversion to staurosporine (**49**) RK-286c (**50**), MLR-52 (**51**), and K252a (**14**) (Link *et al.*).

The synthesis of **49-51** began by converting the K252a precursor (**36**, described above in Example 2) to the corresponding aldehyde via LiBH₄ reduction and then Moffatt oxidation (63% yield overall, Scheme XX). Guided by the α -ketol rearrangement results described above, **50** was exposed to BF₃•Et₂O and the reaction allowed to stir at room temperature for 3 h. Given that the proposed ring-expansion of **50** to **51** could proceed to a mixture of regio- and stereoisomeric products, treatment of (+)-**50** with BF₃•OEt₂ in Et₂O (2.2 equiv, 25- 30 °C, 24h) surprisingly produces a single product, (+)-**51**, in 85% yield. The regio- and stereochemical outcome of this reaction, which were confirmed by spectral comparison to a closely related model and the conversion of (+)-**51** to (+)-**50** (*vide infra*).

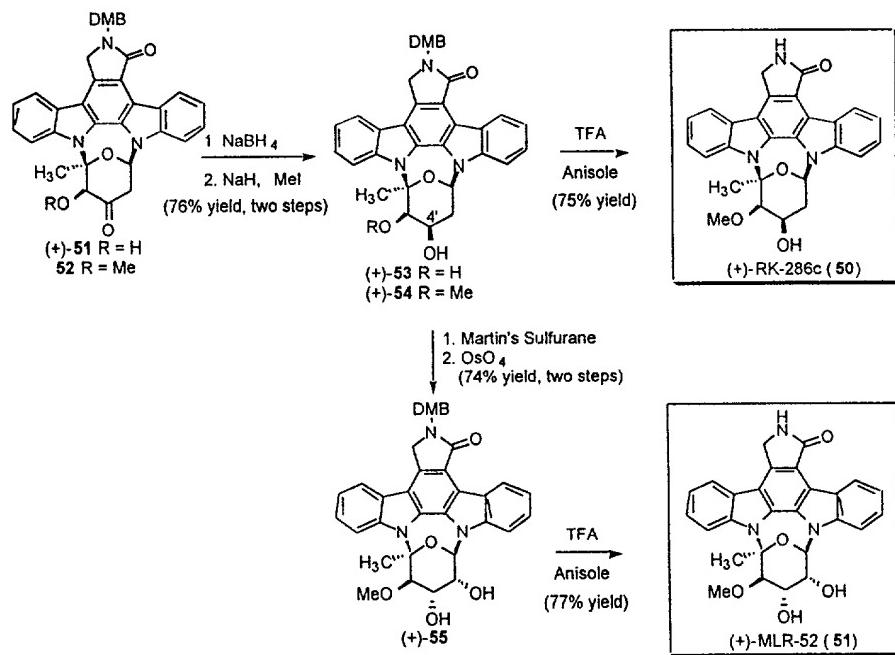
Scheme XX



As expected from the data presented in Example 3, attempts to methylate **51** were unproductive and again led to the observation that exposure of **(+)-51** to CuCl in MeOH results in a highly stereoselective oxidation/ring-contraction sequence that produces **(+)-36** in 95% yield.

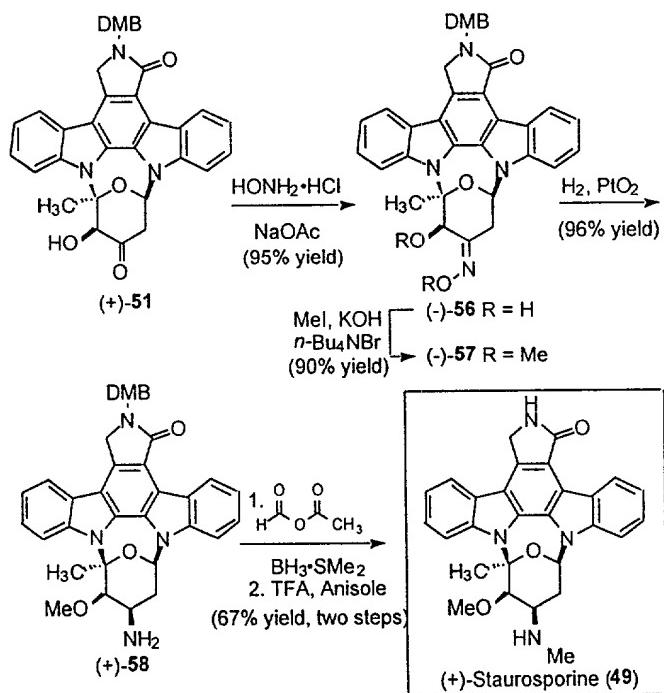
Turning from the potentially biomimetic synthesis of **(+)-K252a** to the synthesis of **49-51**, it was discovered that **(+)-51** undergoes selective conversion to **(+)-54** upon sequential treatment with NaBH₄ and NaH/MeI. Having installed all of the functional groups common to **(+)-50-51**, the approach diverged into the synthesis of **(+)-RK286c** and **(+)-MLR-52**. The former was completed via deprotection of **(+)-54** (TFA/anisole) while the latter required a three-step sequence that was initiated by exposing **(+)-54** to Martin's sulfurane. Oxidation of the derived olefin with OsO₄ followed by deprotection of the resultant diol **(+)-55** produced **(+)-51** (Scheme XXI).

Scheme XXI



The inability to prepare α -methoxy ketone **52** guided an approach to staurosporine along a route wherein the 4' nitrogen is introduced via conversion of **(+)-51** to the corresponding oxime **(-)-56** ($\text{H}_2\text{NOH}\cdot\text{HCl}$, NaOAc , Scheme XXII). Crucial for the success of this approach is the fact that **(-)-56**, unlike ketone **(+)-51**, readily undergoes alkylation to the C(3') methyl ether (MeI , KOH , $n\text{-Bu}_4\text{NBr}$). Stereoselective reduction of the derived methoxy oxime **(-)-57** (H_2 , PtO_2) to the corresponding primary amine (**(+)-58**) followed by monomethylation ($\text{HCO}_2\text{COCH}_3$, $\text{BH}_3\cdot\text{DMS}$) and deprotection (TFA) produced **(+)-staurosporine (49)**.

Scheme XXII



In summary, efforts to devise an efficient synthesis of the pyranosylated indolocarbazoles via a common intermediate [*i.e.*, (+)-36] were successful in delivering (+)-49 (19 steps), (+)-50 (17 steps), and (+)-51 (19 steps). In addition, these investigations have revealed both ring-expansion and -contraction reactivity that may play a central role in the biogenesis of both the furanosylated and pyranosylated members of this important class of natural products.

Experimental procedures for selected compounds in Examples 1 to 4 may be found in international publication number WO 97/07081 to Yale University and Wood, *et al.*, 27 February 1997, filed as PCT/IB96/00987 on 9 August 1996, claiming priority benefit of U.S. application serial number 60/002,164, filed 11 August 1995, which is incorporated by reference.

References

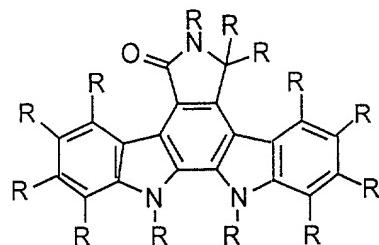
- Fredenhagen, A.; Peter, H.H. *Tetrahedron* 52: 1235 (1996).
- Link, J.T., et al., *J. Am. Chem. Soc.* 115: 3782 (1993).
- Ootsuka, Y. et al. . Jpn. Kokai Tokkyo Koho JP05247054, (1993).
- Omura, S. et al. *J. Antibiotics* 48: 525 (1995).
- McCombie, S.W., et al., *Bioorg. Med. Chem. Lett.* 3: 1537 (1993).
- Pirrung, M.C., et al., *J. Org. Chem.* 60: 2112 (1995).
- Stoltz, B.M., and Wood, J.L., *Tetrahedron Lett.* 36: 8543-8544 (1995).
- Stoltz, B.M., and Wood, J.L., *Tetrahedron Lett.* 37: 3929-3930 (1996).
- Wood, J.L., et al., *J. Amer. Chem. Soc.* 117: 10413-10414 (1995).
- Wood, J.L., et al., *J. Amer. Chem. Soc.* 118:10656-10657 (1996).
- Wood, J.L., et al., *Tetrahedron Lett.* 37:7335-7336 (1996).

All the references cited herein are expressly incorporated herein by reference. The invention was made with partial government support under American Cancer Society grant JFRA-523. The government has certain rights in the invention.

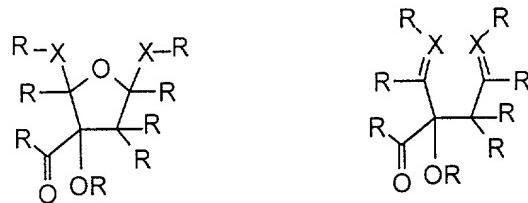
The above description is for the purpose of teaching the person of ordinary skill in the art how to practice the present invention, and it is not intended to detail all those obvious modifications and variations of it which will become apparent to the skilled worker upon reading the description. It is intended, however, that all such obvious modifications and variations be included within the scope of the present invention, which is defined by the following claims. The claims are intended to cover the claimed components and steps in any sequence which is effective to meet the objectives there intended, unless the context specifically indicates the contrary.

Claims

1. A process for the preparation of furanosylated indolocarbazoles by reacting an indolocarbazole of the formula

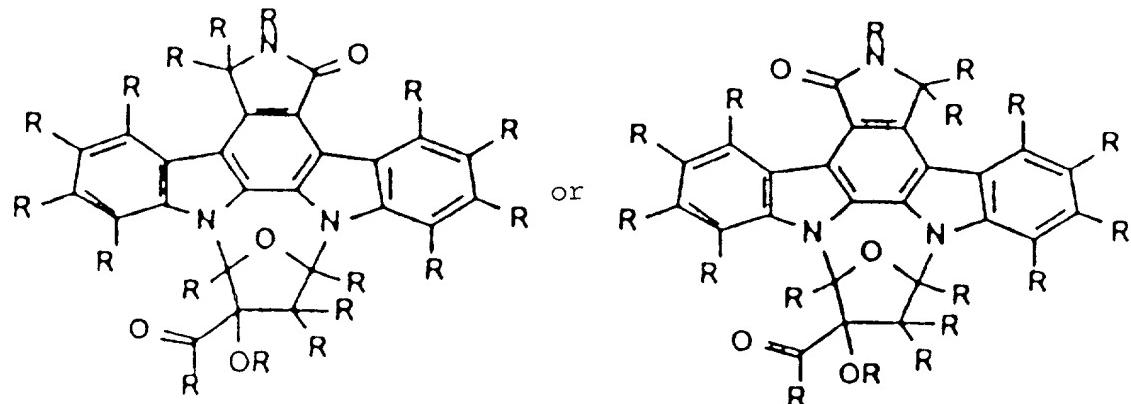


with an acetal selected from the group consisting of the formulae



and mixtures thereof,

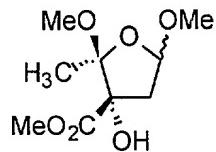
to produce a glycosylated product of the formula



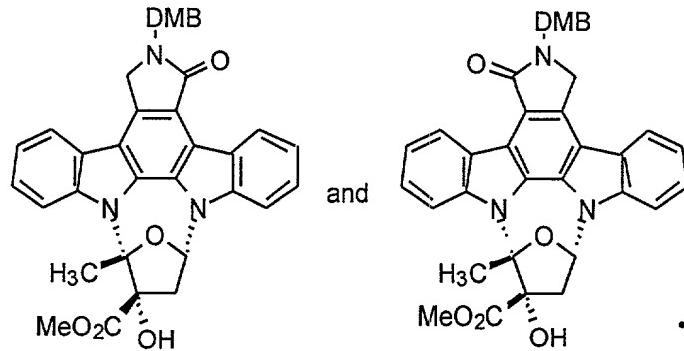
wherein R is selected from the group consisting of

- a) a C₃₋₁₀ branched or unbranched alkyl, optionally partially or fully halogenated, hydroxy, C₁₋₃ alkyloxy, carboxy, amino, alkylamino;
- b) an aryl optionally substituted with one to five groups consisting of halo, hydroxy, C₁₋₃ alkyloxy;
- c) a hydrogen;

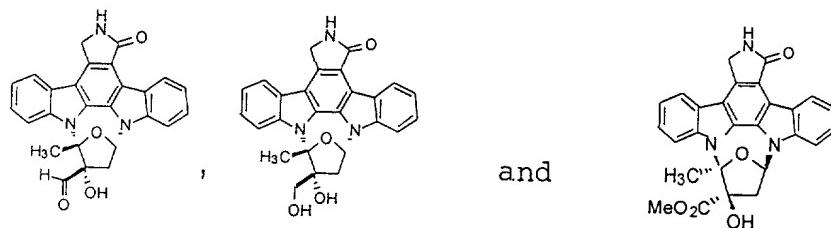
- d) a halogen; and
 - e) mixtures of any of these.
2. A process according to claim 1 wherein the preparation is carried out under conditions that promote acetal exchange or formation.
3. A process according to claim 2 wherein said preparation is carried out in the presence of a Bronsted acid or a Lewis acid.
4. A process according to claim 3 wherein the acid is selected from the group consisting of camphor sulfonic acid, *para*-toluene sulfonic acid, and $\text{BF}_3 \bullet \text{Et}_2\text{O}$.
5. A process according to claim 4 wherein camphor sulfonic acid is used as a catalyst and dichloroethane is used as a solvent.
6. A process according to claim 1 wherein R is selected from the group consisting of H, a halogen, Me, Bu, t-Bu, OH, MeO, CO_2Me , DMB, PMB, NHMe, Bn, NH_2 , OH, and mixtures thereof.
7. A process according to claim 6 wherein R is H, Me, CO_2Me , or OH.
8. A process according to claim 1 wherein a furanose of the formula



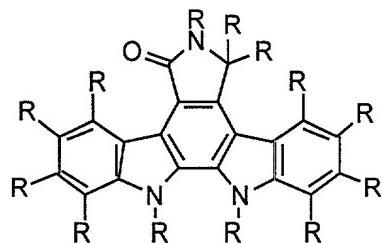
is reacted with DMB-protected K252c to give two products of the formulae



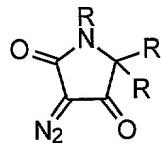
9. A product prepared according to the process of claim 1.
10. A product prepared according to the process of claim 6.
11. A process according to claim 1 wherein the furanosylated indolocarbazole prepared is K252a.
12. A process according to claim 1 wherein the furanosylated indolocarbazoles prepared are selected from the group consisting of:



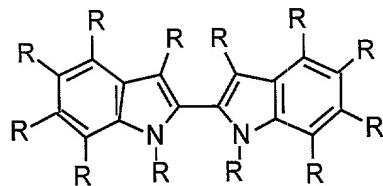
13. A process according to claim 1 wherein the indolocarbazole of the formula



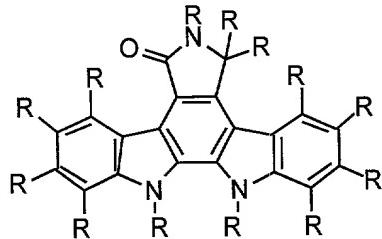
is prepared by reacting a diazo compound of the formula



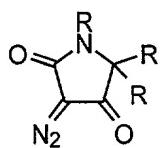
with a biindole of the formula



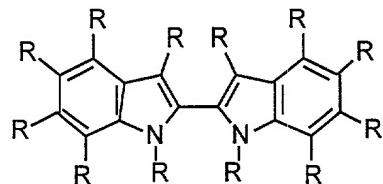
14. A process according to claim 13 wherein the reaction is carried out in the presence of a transition metal catalyst in a solvent capable of solvating the reactants.
15. A process according to claim 13 wherein the coupling reaction is carried out in the presence of a Rh₂(OAc)₄ catalyst.
16. A process according to claim 13 wherein the diazo compound is a diazolaactam and the biindole is a 2,2'-biindole.
17. A process for the preparation of furanosylated indolocarbazoles by first preparing an indolocarbazole of the formula



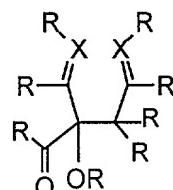
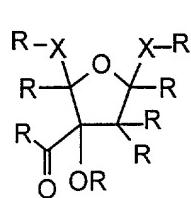
by reacting a diazo compound of the formula



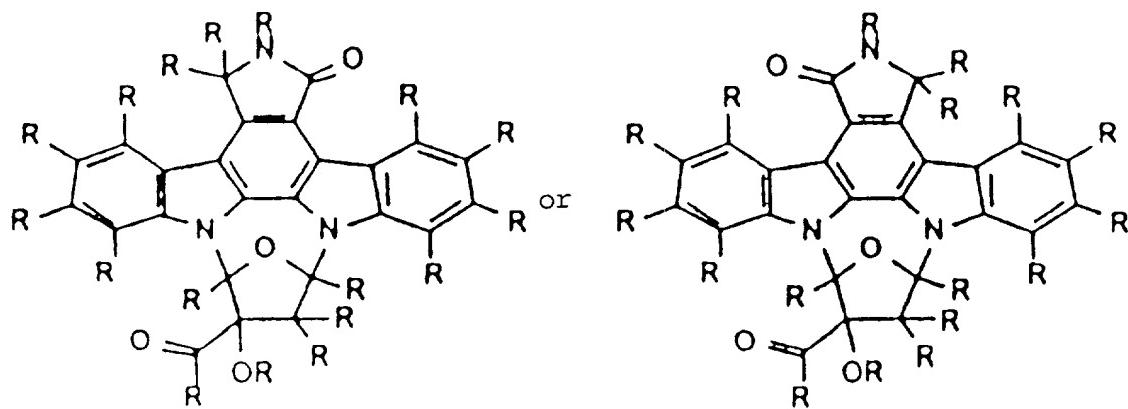
with a biindole of the formula



in the presence of a transition metal catalyst in a solvent capable of solvating the reactants, and then reacting the indolocarbazole with an acetal selected from the group consisting of the formulae



and mixtures thereof, in the presence of a Bronsted acid or a Lewis acid to produce a glycosylated product of the formula



wherein R is selected from the group consisting of a C₃₋₁₀ branched or unbranched alkyl, optionally partially or fully halogenated; an hydroxy; a C₁₋₃ alkyloxy; a carboxy; an amino; an alkylamino; a hydrogen; a halogen; and mixtures of any of these.

18. A process according to claim 17 wherein R is selected from the group consisting of H, a halogen, Me, Bu, t-Bu, OH, MeO, CO₂Me, DMB, PMB, NHMe, Bn, NH₂, OH, and mixtures thereof.

19. A process according to claim 17 wherein the furanosylated indolocarbazole prepared is K252a.

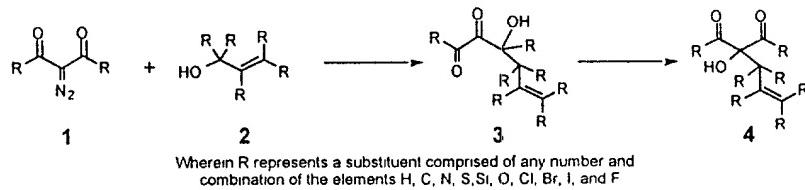
20. A product produced by the process of claim 17.

GLYCOSYLATED INDOLOCARBAZOLE SYNTHESIS

Abstract

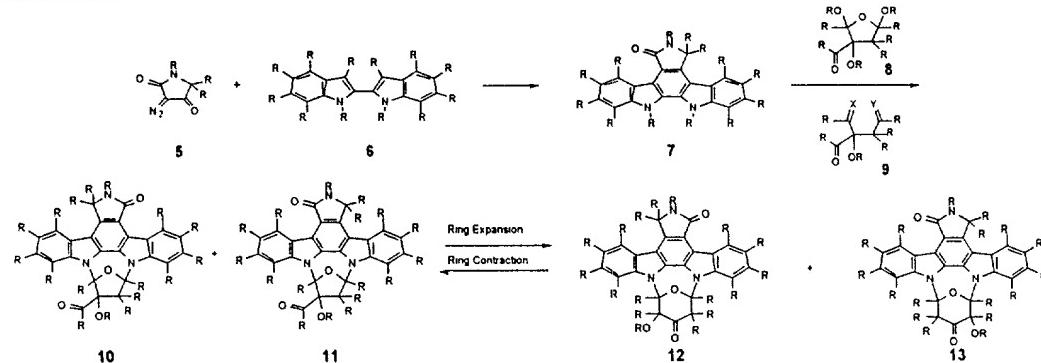
Tertiary alcohols containing the structural features illustrated in 3 or 4 below (Scheme I) are prepared by reacting at least one diazo carbonyl compound, *e.g.*, 1 in Scheme I) and at least one allylic alcohol (*e.g.*, 2 in Scheme I) in a coupling reaction run under conditions that produce carbene or carbenoid intermediates from the diazo-containing substrate such as transition metal catalysis or either thermal or photochemical decomposition. In some preferred embodiments, Rh₂(OAc)₄ is employed to catalyze the coupling reaction.

Scheme I



10 Indolocarbazoles (*e.g.*, 7 below) are prepared by coupling of diazo carbonyl compounds (*e.g.*, 5) and biindoles (*e.g.*, 6). Indolocarbazoles are furanosylated (*e.g.*, 7) with acetals (*e.g.*, 8) or their open chain congeners (*e.g.*, 9) under conditions known to promote acetal exchange or formation, such as protic or Lewis acids. Furanosylated indolocarbazoles (*e.g.*, 10) are also prepared via ring contraction of pyranosylated indolocarbazoles (*e.g.*, 11) under conditions known to effect oxidation and benzylic acid type rearrangements, and pyranosylated indolocarbazoles (*e.g.*, 11) are prepared via ring expansion of the furanosylated congeners (*e.g.*, 10).

Scheme II



Separator Sheer



III

Miscellaneous Material Includes:

- 1. Drawings**
- 2. Oath or Declaration**
- 3. Foreign language specification**
- 4. Sequence listing**
- 5. Computer listing**
- 6. Appendices**

DECLARATION AND POWER OF ATTORNEY

As below-named inventors, we hereby declare that:

Our residences, post office addresses, and citizenships are as stated below next to our names.

We believe that we are the original, first and sole inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled "**Glycosylated Indolocarbazole Synthesis**", International Application Publication No. 97/07081, published 27 February 1997, and filed as a national phase application, Serial No. 08/817,230 on 11 April 1997.

We hereby state that we have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. To the best of our knowledge, information, and belief the facts stated therein are true.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56.

We hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign applications for patent or inventor's certificate listed below.

PCT/IB96/00987 Filed August 9, 1996

We hereby claim the benefit under Title 35, United States Code, §120 of the following United States Applications listed below, and insofar as the subject matter of each of the claims of this Application is not disclosed in the prior United States Application in the manner provided by the first paragraph of Title 35, United States Code, §112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56 which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

US - Application No. 60/002,164 Filed August 11, 1995

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

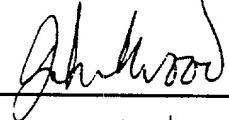
Page 2
Declaration and
Power of Attorney

We hereby appoint Mary M. Krinsky, Registration No. 32,423, of ST. ONGE STEWARD JOHNSTON & REENS LLC; 986 Bedford Street; Stamford, Connecticut 06905-5619 (203 324-6155); with full power of substitution, association and revocation, as attorney to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

Please direct all telephone calls and correspondence to Mary M. Krinsky at the above address and telephone number.

Full name of first inventor:

John L. Wood



Inventor's signature

Date:

4/18/97

Residence:

Hamden, Connecticut

Citizenship:

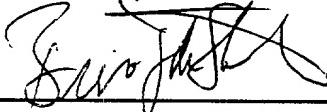
A citizen of United States of America

Post Office Address:

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Hamden, CT 06517

Full name of
second joint inventor:

Brian M. Stoltz



Inventor's signature

Date:

4/18/97

Residence:

New Haven, Connecticut

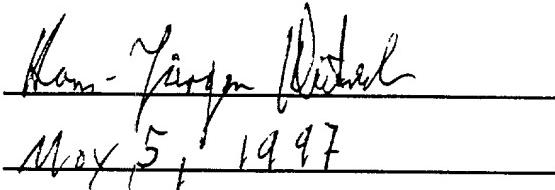
Citizenship:

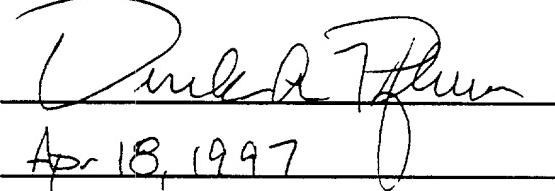
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Page 3
Declaration and
Power of Attorney

Full name of
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Full name of
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